Pharmacology

Drugs That Affect The:

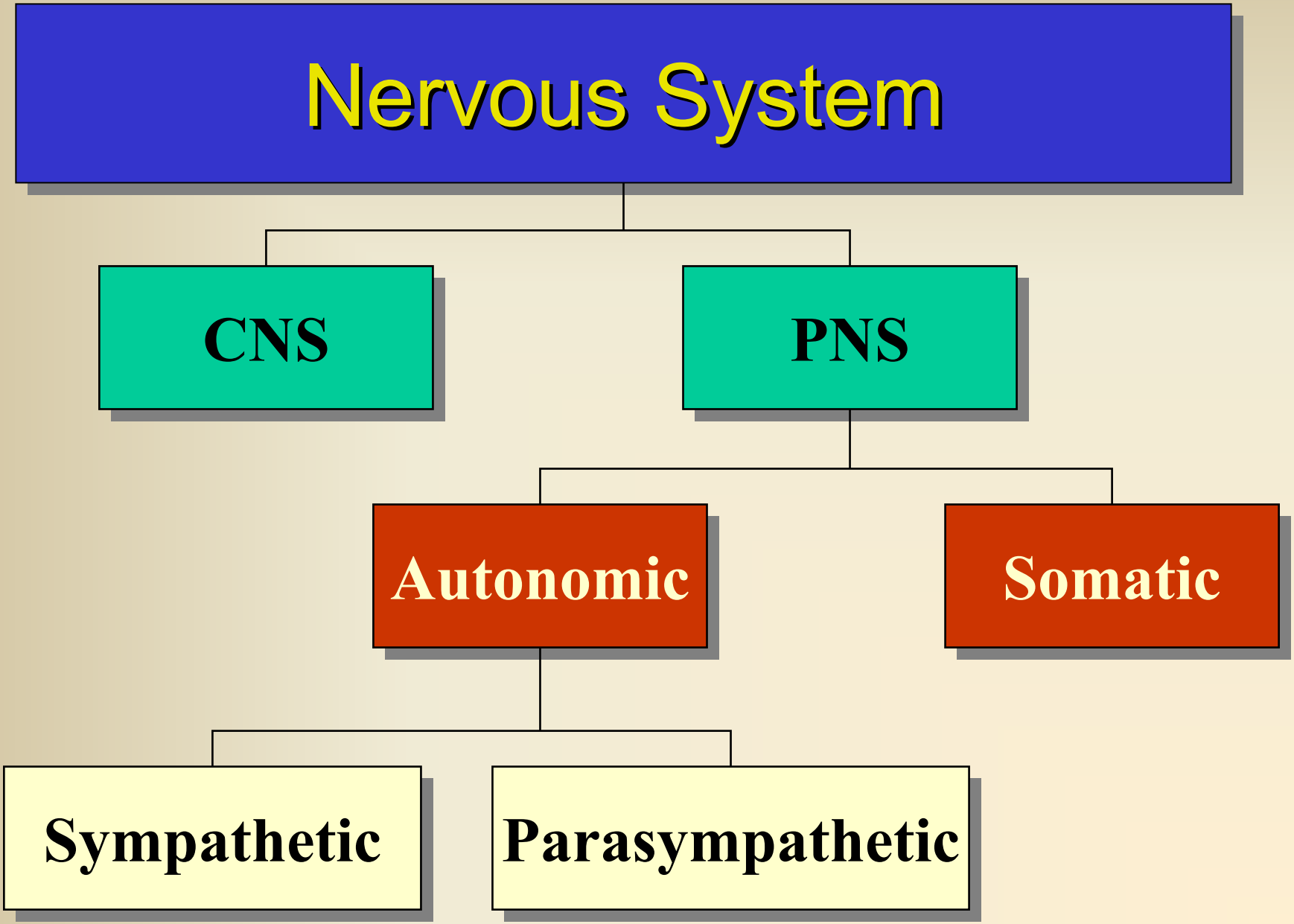
Nervous System

Topics

- Analgesics and antagonists
- Anesthetics
- Anti-anxiety and sedative-hypnotics
- Anti-seizure / anti-convulsants
- CNS stimulators
- Psychotherapeutics
- ANS/PNS/SNS agents

But first...

A colorful review of neurophysiology!


Nervous System
CNS
PNS
Autonomic
Somatic
Sympathetic
Parasympathetic

Analgesics

- Decrease in sensation of pain.
- Classes:
  - Opioid.
    - Agonist.
    - Antagonist.
    - Agonist-antagonist.
  - Non-opioids.
    - Salicylates.
    - NSAIDs.
    - Adjuncts.

Opioids

- Generic reference to morphine-like drugs/actions
  - Opiate: derivative of opium
- Prototype: morphine
  - Morpheus: god of dreams
- Act on endorphin receptors:
  - Mu (most important)
  - Kappa

Actions of Opioid Receptors

Response	Mu	Kappa
Analgesia	☑	☑
Respiratory Depression	☑	
Sedation	☑	☑
Euphoria	☑	
Physical Dependence	☑	
⇓ GI motility	☑	☑

Actions at Opioid Receptors

Drugs	Mu	Kappa
Pure Agonists -morphine, codeine, meperidine (Demerol®), fentanyl (Sublimaze®), remifentanil (Ultiva®), propoxyphene (Darvon®), hydrocodone (Vicodin®), oxycodone (Percocet®)	Agonist	Agonist
Agonist-Antagonist -nalbuphine (Nubaine®), butorphanol (Stadol®)	Antagonist	Agonist
Pure Antagonist -naloxone (Narcan®)	Antagonist	Antagonist

General Actions of Opioids

- Analgesia
- Respiratory depression
- Constipation
- Urinary retention
- Cough suppression
- Emesis
- Increased ICP
  - Indirect through CO_2 retention

- Euphoria/Dysphoria
- Sedation
- Miosis
  - Pupil constriction
- ⇓ Preload & afterload
  - Watch for hypotension!

Non-opioid Analgesics

- Salicylates
  - Aspirin (Bayer®) * (prototype for class)
- Non-Steroidal Anti-Inflammatory Drugs
    - Ibuprofen (Motrin®, Advil®)
      - Propionic Acid derivative
    - Naproxen (Naprosyn®)
    - Naproxen sodium (Aleve®)
    - All compete with aspirin for protein binding sites
  - Ketorolac (Toradol®)

NSAID Properties

Drug	Fever	Inflammation	Pain
Aspirin	☑	☑	☑
Ibuprofen	☑	☑	☑
Acetaminophen	☑		☑

Aspirin Mechanism of Action

- Inhibit synthesis of cyclooxygenase (COX)
  - Enzyme responsible for synthesis of:

Prostaglandins
–Pain response
–Suppression of gastric acid secretion
–Promote secretion of gastric mucus and bicarbonate
–Mediation of inflammatory response
–Production of fever
–Promote renal vasodilation (⇑ blood flow)
–Promote uterine contraction

Thromboxane A_2
–Involved in platelet
–aggregation

Aspirin Effects

Good

- Pain relief
- ⇓ Fever
- ⇓ Inflammation

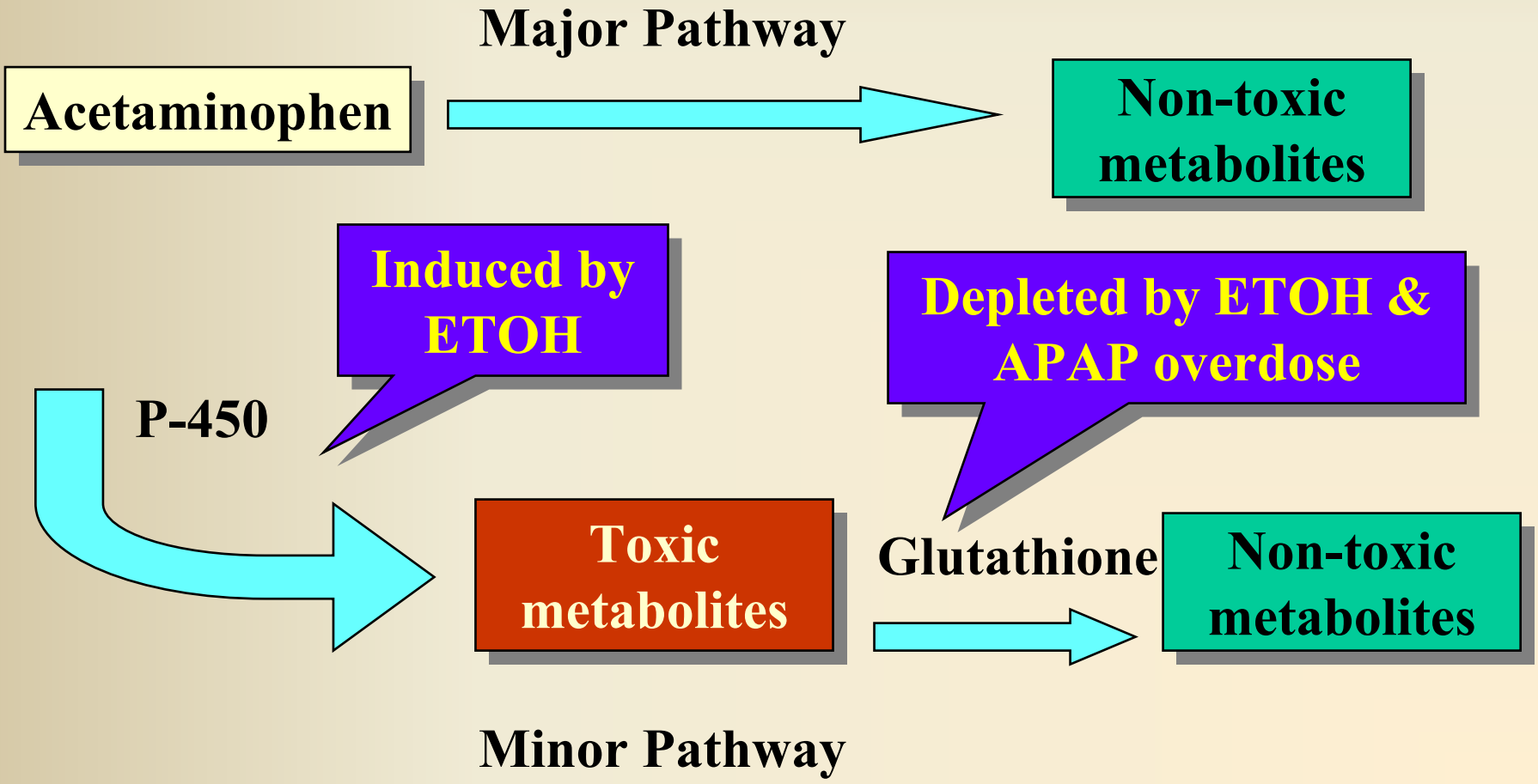
Bad

- GI ulceration:
  - ⇑ Gastric acidity
  - ⇓ GI protection
- ⇑ Bleeding
- ⇓ Renal elimination
- ⇓ Uterine contractions during labor

Acetaminophen (Tylenol®)

- NSAID similar to aspirin
- Only inhibits synthesis of CNS prostaglandins
  - Does not have peripheral side effects of ASA:
    - Gastric ulceration
    - ⇓ Platelet aggregation
    - ⇓ Renal flow
    - ⇓ Uterine contractions

Acetaminophen Metabolism



Anesthetics

- Loss of all sensation
  - Usually with loss of consciousness
  - ⇓ propagation of neural impulses
- General anesthetics
  - Gases
    - Nitrous oxide (Nitronox®), halothane, ether
  - IV
    - Thiopental (Pentothal®), methohexital (Brevitol®), diazepam (valium®), remifentanil (Ultiva®)

Anesthetics

- Local
  - Affect on area around injection
  - Usually accompanied by epinephrine
    - Lidocaine (Xylocaine ®), topical cocaine

Anti-anxiety & Sedative-hypnotic Drugs

- Sedation: ⇓ anxiety & inhibitions
- Hypnosis: instigation of sleep
- Insomnia
  - ⇑ Latent period
  - ⇑ Wakenings
- Classes:
  - Barbiturates
  - Benzodiazepines
  - Alcohol

Chemically different, Functionally similar

Mechanism of action

- Both promote the effectiveness of GABA receptors in the CNS
  - Benzodiazepines promote only
  - Barbiturates promote and (at high doses) stimulate GABA receptors
- GABA = chief CNS inhibitory neurotransmitter
  - Promotes hyperpolarization via ⇑ Cl^- influx

Benzodiazepines vs. Barbiturates

Criteria	BZ	Barb.
Relative Safety	High	Low
Maximal CNS depression	Low	High
Respiratory Depression	Low	High
Suicide Potential	Low	High
Abuse Potential	Low	High
Antagonist Available?	Yes	No

Benzodiazepines

Benzodiazepines

- diazepam (Valium®)
- midazolam (Versed®)
- alprazolam (Xanax®)
- lorazepam (Atiavan®)
- triazolam (Halcion®)

"Non-benzo benzo"

- zolpidem (Ambien®)
- buspirone (BusPar®)

Barbiturates

Subgroup	Prototype	Typical Indication
Ultra-short acting	thiopental (Pentothol®)	Anesthesia
Short acting	secobarbital (Seconal®)	Insomnia
Long acting	phenobarbital (Luminal®)	Seizures

Barbiturates

- amobarbital (Amytal®)
- pentobarbital (Nembutal®)
- thiopental (Pentothal®)
- phenobarbital (Luminal ®)
- secobarbital (Seconal ®)

Anti-seizure Medications

- Seizures caused by hyperactive brain areas
- Multiple chemical classes of drugs
  - All have same approach
  - Decrease propagation of action potentials
    - $\Downarrow Na^{+}$, Ca^{++} influx (delay depolarization/prolong repolarization)
    - $\Uparrow Cl^{-}$ influx (hyperpolarize membrane)

Anti-Seizure Medications

Benzodiazepines

- diazepam (Valium®)
- lorazepam (Ativan®)

Barbiturates

- phenobarbital (Luminal®)

Ion Channel Inhibitors

- carbamazepine (Tegretol®)
- phenytoin (Dilantin®)

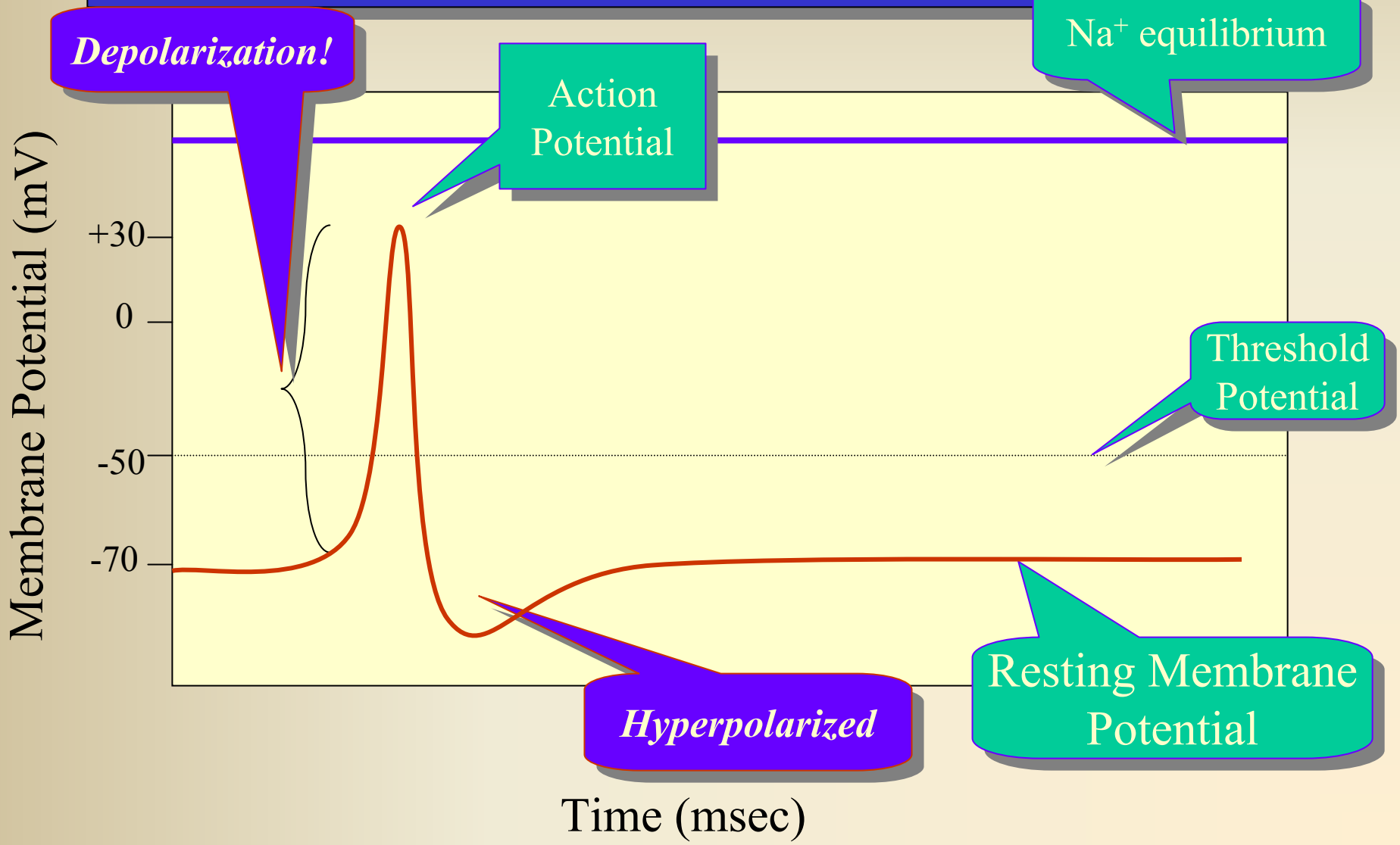
Misc. Agents

- valproic acid (Depakote®)

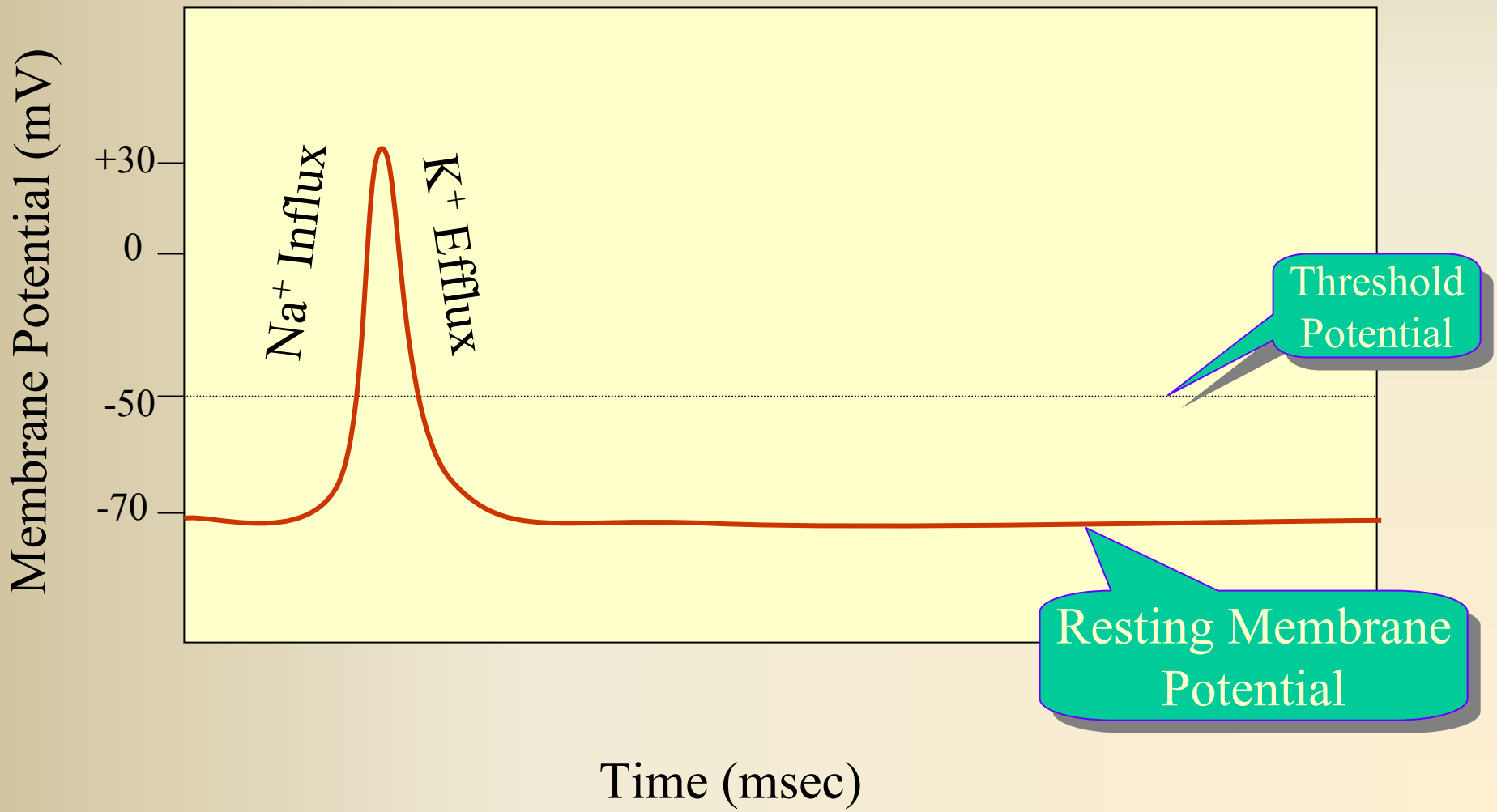
Ion Diffusion

- Key to neurophysiology
- Dependent upon:
  - Concentration gradient
  - Electrical gradient
- Modified by:
  - ‘Gated ion channels’

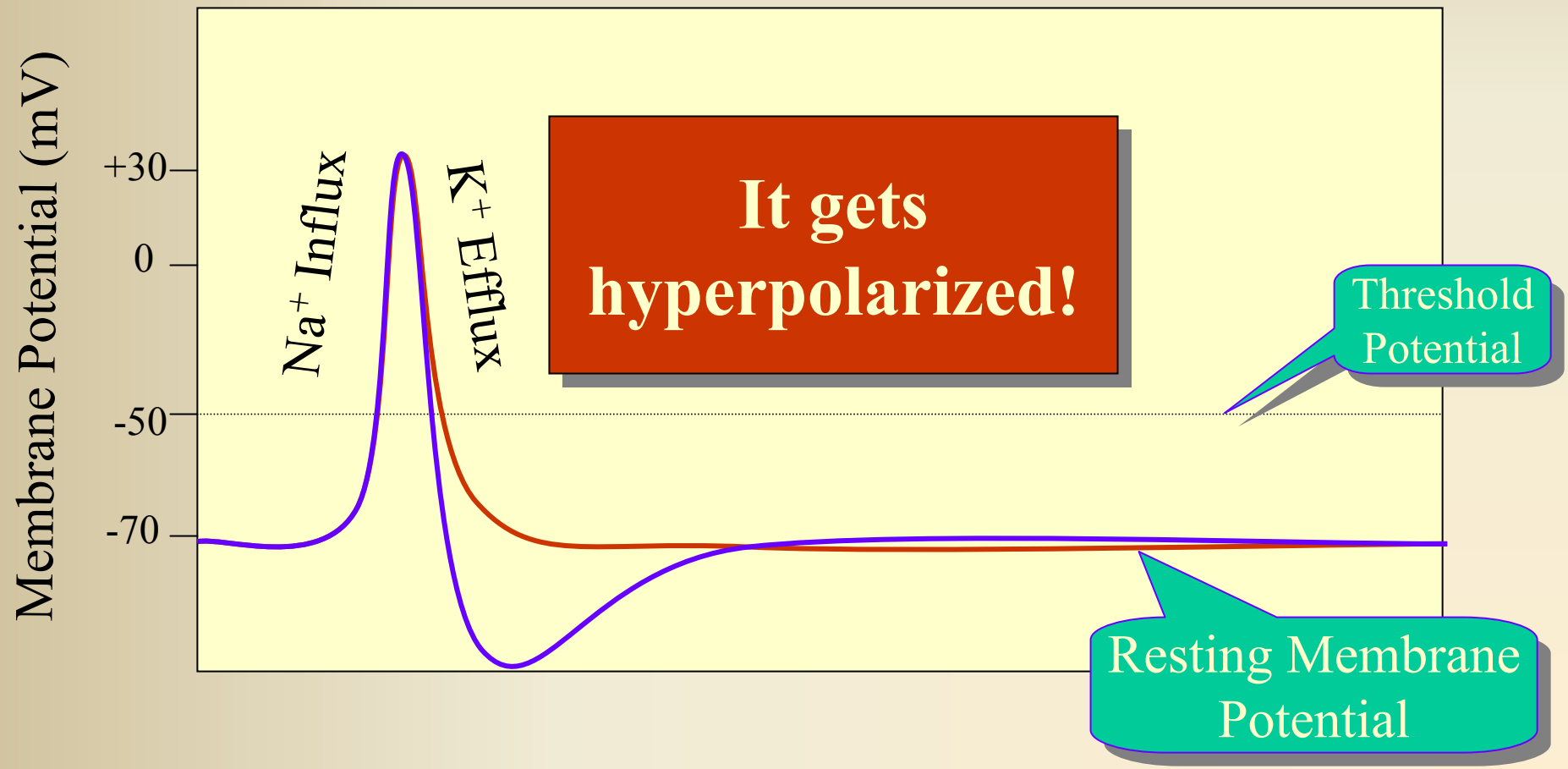
Action Potential Components



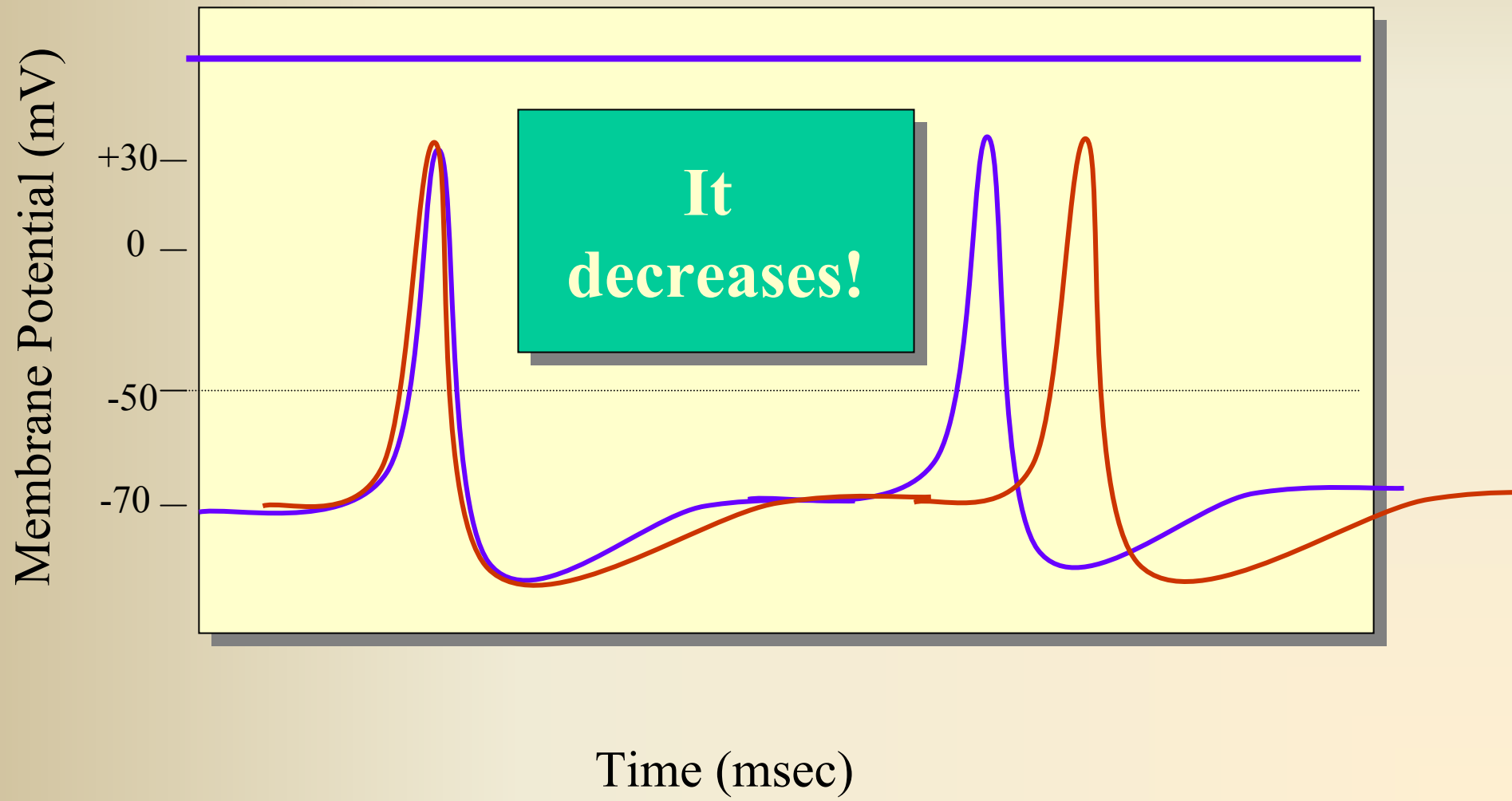
Membrane Permeability



What Happens to the Membrane If Cl^- Rushes Into the Cell During Repolarization?



What Happens to the Frequency of Action Potentials If the Membrane Gets Hyperpolarized?



Clinical Correlation

- Remember that it is the rate of action potential propagation that determines neurologic function.
  - Determined by frequency of action potentials.

What would be the effect on the membrane of ⇑ Cl^- influx during a seizure?

What is a seizure?

Hyperpolarization & ⇓ seizure activity!

Are You Ready for a Big Surprise?

Many CNS drugs act on GABA receptors to effect the frequency and duration of action potentials!

SNS Stimulants

- Two general mechanisms:
  - Increase excitatory neurotransmitter release
  - Decrease inhibitory neurotransmitter release

- Three classes:
  - Amphetamines
  - Methylphendidate
  - Methylxanthines

Amphetamines

amphetamine

methamphetamine

dextroamphetamine (Dexedrine®)

MOA:

promote release of norepinephrine, dopamine

Indications

- Diet suppression
- ⇓ Fatigue
- ⇑ Concentration

Side Effects

- Tachycardia
- Hypertension
- Convulsion
- Insomnia
- Psychosis

Methylphenidate (Ritalin®)

- Different structure than other stimulants
  - Similar mechanism
  - Similar side effects
- Indication: ADHD
  - Increase ability to focus & concentrate

Methylxanthines

- Caffeine
- Theophylline (Theo-Dur®)
- Aminophylline

Mechanism of action

- Reversible blockade of adenosine receptors

A patient is taking theophylline and becomes tachycardic (SVT). You want to give her adenosine. Is there an interaction you should be aware of? How should you alter your therapy?

Methylxanthines blocks adenosine receptors. A typical dose of adenosine may not be sufficient to achieve the desired result.

Double the dose!

News You Can Use…

Source	Amount of Caffeine
Coffee •Brewed •Instant	 40 – 180 mg/cup 30 – 120 mg/cup
Decaffeinated Coffee	2 - 5 mg/cup
Tea	20 – 110 mg/cup
Coke	40 – 60 mg/12 oz

Psychotherapeutic Medications

- Dysfunction related to neurotransmitter imbalance.
  - Norepinephrine.
  - Dopamine.
  - Seratonin.

  } ***Monoamines***

- Goal is to regulate excitory/inhibitory neurotransmitters.

Anti-Psychotic Drugs (Neuroleptics)

- Schizophrenia
  - Loss of contact with reality & disorganized thoughts
  - Probable cause: increased dopamine release
  - Tx. Aimed at decreasing dopamine activity

Two Chemical Classes:

- **Phenothiazines**
  - **chlorpromazine (Thorazine ®)**
- **Butyrophenones**
  - haloperidol (Haldol®)

Other Uses for Antipsychotics

- Bipolar depression
- Tourette's Syndrome
- Prevention of emesis
- Dementia (OBS)
- Temporary psychoses from other illness

Antipsychotic MOA

- Mechanism is similar
- Strength ([]) vs. Potency ('oomph')
  - Phenothiazines – low potency
  - Butyrophenones – high potency
- Receptor Antagonism
  - Dopamine$_2$ in brain → *Therapeutic effects*
  - Muscarinic cholinergic
  - Histamine
  - Norepi at alpha$_1$

  } *Uninteded effects*

Antipsychotic Side Effects

- Generally short term
- Extrapyramidal symptoms (EPS)
- Anticholinergic effects (atropine-like)
  - Dry mouth, blurred vision, photophobia, tachycardia, constipation)
- Orthostatic hypotension
- Sedation
- Decreased seizure threshold
- Sexual dysfunction

Extrapyramidal Symptoms

Reaction	Onset	Features
Acute dystonia	Hours to 5 days	Spasm of tongue, neck, face & back
Parkinsonism	5 – 30 days	Tremor, shuffling gait, drooling, stooped posture, instability
Akathesia	5 – 60 days	Compulsive, repetitive motions; agitation
Tarditive dyskinesia	Months to years	Lip-smacking, worm-like tongue movement, ‘fly-catching’

Treatment of EPS

- Likely caused by blocking central dopamine$_2$ receptors responsible for movement
- Anticholinergic therapy rapidly effective
  - diphenhydramine (Benadryl®)

Antipsychotic Agents

- chlorpromazine (Thorazine®)
- thioridazine (Mellaril®)
- trifluoperazine (Stelazine®)
- haloperidol (Haldol®)

Antidepressants

- Likely cause: inadequate monoamine levels
- Treatment options:
  - Increasing NT synthesis in presynaptic end bulb
  - Increasing NT release from end bulb
  - Blocking NT ‘reuptake’ by presynaptic end bulb

Tricyclic Antidepressants (TCAs)

- Block reuptake of both NE & serotonin
  - Enhance effects
- Similar side effects to phenothiazines

TCA Side Effects

- Orthostatic hypotension
- Sedation
- Anticholinergic effects
- Cardiac toxicity
  - Ventricular dysrythmias

Selective Serotonin Reuptake Inhibitors (SSRIs)

- Block only serotonin (not NE) reuptake
  - Elevate serotonin levels
- Fewer side effects than TCS
  - No hypotension
  - No anticholinergic effects
  - No cardiotoxicity
- Most common side effect
  - Nausea, insomnia, sexual dysfunction

Monoamine Oxidase Inhibitors (MAOIs)

- Monoamine oxidase
  - Present in liver, intestines & MA releasing neurons
  - Inactivates monoamines
  - Inactivates dietary tyramine in liver
    - Foods rich in tyramine: cheese & red wine

MAOI Side Effects

- CNS Stimulation
  - Anxiety, agitation
- Orthostatic hypotension
- Hypertensive Crisis
  - From increased tyramine consumption
    - Excessive arteriole constriction, stimulation of heart

Antidepressants Agents

TCAs

- imiprimine (Tofranil®)
- amitriptyline (Elavil®)
- nortriptyline (Pamelor ®)

SSRIs

- fluoxetine (Prozac®)
- paroxetine (Paxil®)
- sertraline (Zoloft®)

MAOIs

- phenelzine (Nardil®)

Atypical Antidepressants

- bupropion (Wellbutrin®)

Parkinson's Disease

- Fine motor control dependent upon balance between excitatory and inhibitory NT
  - Acetylcholine = excitatory
  - Dopamine =inhibitory

  } Control GABA release

  GABA= inhibitory

Parkinson's Symptoms:

- Similar to EPS
- Dyskinesias
  - Tremors, unsteady gait, instability
- Bradykinesia
- Akinesia in severe cases

Parkinson's Treatment

- Dopaminergic approach
  - ⇑ Release of dopamine
  - ⇑ [Dopamine]
  - ⇓ Dopamine breakdown
- Cholinergic approach
  - ⇓ Amount of ACh released
  - Directly block ACh receptors
- All treatment is symptomatic and temporary

Levodopa

- Sinemet ® = levodopa + carbidopa
- Increase central dopamine levels
- Side effects:
  - Nausea and vomiting
  - Dyskinesia (~80% of population)
  - Cardiovascular (dysrythmias)

Other Agents

- amantadine (Symmetrel®)
  - – ⇑ release of dopamine from unaffected neurons
- bromocriptine (Parlodel®)
  - – Directly stimulated dopamine receptors
- selegiline (Carbex®, Eldepryl®)
  - – MAOI selective for dopamine (MAO-B)
- benztropine (Cogentin®)
  - – Centrally acting anticholinergic

Drugs That Affect the Autonomic Nervous System

Word of Warning

Carefully review the A&P material & tables on pages 309 – 314 and 317 – 321!

PNS Drugs

- Cholinergic
  - Agonists & Antagonistis (Anticholinergics)
  - Based on response at nicotinic$_{(N\&M)}$ & muscarinic receptors

Cholinergic Agonists

Cholinergic agents cause <u>SLUDGE</u>!

<u>HINT!</u>
These effects are predictable by knowing PNS physiology (table 9-4)

<u>S</u>alivation
<u>L</u>acrimation
<u>U</u>rination
<u>D</u>efecation
<u>G</u>astric motility
<u>E</u>mesis

Direct Acting Cholinergics

- bethanechol (Urecholine) prototype
  - Direct stimulation of ACh receptors
  - Used for urinary hesitancy and constipation

Indirect Acting Cholinergics

- Inhibit ChE (cholinesterase) to prolong the duration of ACh stimulation in synapse
- Reversible
- Irreversible

Reversible ChE Inhibitors

- neostigmine (Prostigmine®)
  - Myasthenia Gravis at nicotinic$_M$ receptors
  - Can reverse nondepolarizing neuromuscular blockade
- physostigmine (Antilirium®)
  - Shorter onset of action
  - Used for iatrogenic atropine overdoses @ muscarinic receptors

Irreversible ChE Inhibitors

- Very rarely used clinically
- Very common in insecticides & chemical weapons
  - VX and Sarin gas
  - Cause SLUDGE dammit and paralysis
- Tx: atropine and pralidoxime (2-PAM®)
  - Anticholinergics

Anticholinergics

- Muscarinic antagonists
  - Atropine
- Ganglionic antagonists
  - block nicotinic$_N$ receptors
  - *Turns off the ANS!*
  - trimethaphan (Arfonad®)
    - Hypertensive crisis

- Atropine Overdose
  - Dry mouth, blurred vision, anhidrosis

Hot as Hell

Blind as a Bat

Dry as a Bone

Red as a Beet

Mad as a Hatter

Neuromuscular Blockers

- Nicotinic Cholinergic Antagonists
  - Given to induce paralysis
- Depolarizing
  - succinylcholine (Anectin®)
- Nondepolarizing
  - tubocurarine from *curare*
  - rocuronium (Zemuron®)
  - vecuronium (Norcuron®)

Warning!

- Paralysis without loss of consciousness!
  - MUST also give sedative-hypnotic
  - Common agents:
    - fentanyl (Sublimaze®)
    - midazolam (Versed®)

SNS Drugs

- Predictable response based on knowledge of affects of adrenergic receptor stimulation
- HINT: Know table 9-5, page 321
- Each receptor may be:
  - Stimulated (sympathomimetic)
  - Inhibitied (sympatholytic)

Alpha$_1$ Agonists

- Profound vasoconstriction
  - Increases afterload & blood pressure when given systemically
  - Decreases drug absorption & bleeding when given topically

Alpha$_1$ Antagonism

- Inhibits peripheral vasoconstriction
  - Used for hypertension
  - prazosin (Minipress®)
  - doxazosin (Cardura®)
  - phentolamine (Regitine®)
    - Blocks alpha$_{1\&2}$ receptors

$Beta_1$ Agonists

- Increases heart rate, contractility, and conductivity

Beta Antagonists (β Blockers)

- Frequently used
- Lower Blood Pressure
- Negative chronotropes & inotropes

<u>$Beta_1$ Selective Blockade</u>

- atenolol (Tenormin®)
- esmolol (Brevibloc®)
- metoprolol (Lopressor®)

<u>Nonselective</u>

- propranolol (Inderal®)
- labetalol (Normodyne®, Trandate®)
- sotalol (Betapace®)

Adrenergic Receptor Specificity

Drug	α_1	α_2	β_1	β_2	Dopaminergic
Epinephrine	←			→	
Ephedrine	←			→	
Norepinephrine	←		→		
Phenylephrine	↔				
Isoproterenol			←	→	
Dopamine	↔		←	→	
Dobutamine			↔		
terbutaline				↔	

Web Resources

- Web based synaptic transmission project
  - http://www.williams.edu/imput/index.html